populations and the heterogeneous etiology of the recurrent pericarditis. Clearly, there is a need for an international, randomized study to test the effectiveness of colchicine and other treatments, for example, intrapericardial triamcinolone administration tested by Maisch et al. (3). The evaluation of the effectiveness of treatments is difficult on the basis of single cases, as the course of recurrent pericarditis is unpredictable although gradually "burning out." The chronicity of the condition is exemplified by two of our patients believed to be cured of the disease, but who after the acceptance of our article have had new relapses after 9 and 11 years' quiescence, respectively.

Similar to Dr. Brucato and his colleagues, we find it important to use as nontoxic drugs as possible during the acute phases of pericarditis. However, our experience in young patients does not support their recommendation of routine multidrug therapy including long-term corticosteroids, colchicine, and NSAIDs. In our hands, mere NSAID treatment was in the long run at least as effective as the treatment with different immunosuppressive drugs.

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Time Course of the Interaction Between Tadalafil and Nitrates

The Express Publication by Kloner et al. (1) on the interactions between nitrates and tadalafil should be of interest to all cardiologists and physicians seeing patients with acute chest pain.

However, I have several questions: 1) What is the duration of erectile dysfunction efficacy of tadalifil? The long half-life suggests that responsiveness to the drug may last 2 to 3 days; do we know whether the blood pressure and heart rate effects of nitrates with tadalafil on board are concordant with the duration of improvement in sexual function? 2) It is unclear whether there is a repeat run-in of 7 days for both placebo and tadalafil after the cross-over, that is, is the second-half dosing the same as the first part of the protocol? 3) Why is the recommendation made to withhold concomitant use of a nitrate and tadalafil for 48 h when all data robustly support no interaction at this time interval? 4) The half-life of sildenafil, the gold standard phosphodiesterase 5 (PDE5) inhibitor is not provided. This would be useful, including the best estimate of its duration of its action, as well as the time period during which there is a potentially hazardous interaction between this PD5 inhibitor and nitrates. 5) Is it possible that an acute dosing interaction (no previous exposure for several days) with nitrates with sildenafil or tadalafil might induce a different response to nitrates than after 5 to 6 consecutive half-lives of the PD5 inhibition? Thus, it may be that a form of tolerance to nitrate hemodynamic effects could develop within days in the vasculature, attenuating the decrease in blood pressure and increase in heart rate after an individual has been taking a PD5 inhibitor for a considerable amount of time, as in this experiment. The protocol design does not really mirror the way sildenafil and tadalafil are used in daily living. It would be useful to know if there are data that answer these questions.

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REPLY

We would like to thank Dr. Abrams for his questions regarding our study on the time course of the interaction between tadalafil and sublingual nitroglycerin (SL-NTG) (1). In response to question 1 regarding the duration of efficacy: Since the publication of the article (1), tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, has been approved by the Food and Drug Administration for the treatment of erectile dysfunction (ED) (2). Tadalafil improves erectile function in men with ED for up to 36 h after dosing (2,3). Therefore, the duration of efficacy of tadalafil for the treatment of ED for up to 36 h is similar to the time course of the interaction of tadalafil with nitrates (i.e., the hemodynamic interaction between tadalafil and SL-NTG lasted 24 h but was not seen at 48 h and beyond).

In response to question 2 regarding study design: Our study was a randomized, placebo-controlled, double-blind, two-period, cross-over, multicenter study (n = 150). During treatment period 1, subjects received seven consecutive daily doses of either tadalafil (20 mg) or placebo before SL-NTG administration. After a 10- to 21-day washout period, subjects were crossed over to the opposite treatment (treatment period 2) and received seven consecutive daily doses of either tadalafil or placebo before SL-NTG administration.

In response to question 3 regarding the recommendation to withhold nitrates for 48 h: In our study, SL-NTG (0.4 mg) was administered at 2, 4, 8, 24, 48, 72, and 96 h after the last dose of tadalafil 20 mg or placebo. Tadalafil augmented the blood pressure-lowering effects of SL-NTG from 2 to 24 h post-dosing

compared with placebo, with no significant differences at 48, 72, or 96 h. Our study did not examine the time points between 24 and 48 h to assess when the hemodynamic interaction between tadalafil and SL-NTG was no longer detectable. Therefore, if deemed medically necessary, nitrates should be administered only under close medical supervision with hemodynamic monitoring at 48 h and beyond the last dose of tadalafil.

In response to question 4 regarding the half-life of sildenafil: The half-life of sildenafil is 4 h (4). Several studies have demonstrated the interaction between sildenafil and organic nitrates (5–7). Recently, a preliminary study (7) performed in 33 healthy men showed that SL-NTG, administered at multiple time points up to 48 h post-sildenafil 100 mg or placebo dosing, produced decreases in mean sitting blood pressure that were significantly different (sildenafil minus placebo) only at 1 h post-sildenafil or placebo dosing. Although the experimental design was similar to our clinical trial (1), the sildenafil study only reported mean blood pressures. Because interactions may be missed by only analyzing mean changes in blood pressure, the number of patients with potentially clinically significant blood pressure changes (i.e., 'outliers') should also be used to detect hemodynamic interactions (1,8,9). This preliminary sildenafil study (7) was also much smaller than our study and was performed in healthy men only. Because of the potential for clinically relevant hypotension, the American College of Cardiology/American Heart Association Consensus Committee recommends that nitrates not be given until 24 h (5 to 6 half-lives) after taking sildenafil (4).

In response to question 5 regarding the non–steady-state dosing of tadalafil: We examined the hemodynamic effects of SL-NTG administered after single doses of tadalafil (5 mg and 10 mg) compared with placebo (8–10). These studies examined both mean maximal changes in blood pressure as well as blood pressure outlier data. Although not performed within the same study, the hemodynamic interactions with nitrates after a single dose of tadalafil were comparable to those after steady-state dosing of tadalafil (1,8–10). Studies have not been done to examine the development of tolerance to the hemodynamic effects of nitrates in the presence of PDE5 inhibitors. Importantly, nitrates are contraindicated whether a patient has been taking daily or intermittent doses of any PDE5 inhibitor (e.g., tadalafil, sildenafil, or vardenafil).

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